



CCTGACCGGGCCGGCGGCCTCCCCGGGTCTCGCCCCCTCTACCGAGCGCCTCGCCGCC
CCCTCCCCGGCCCGCTCCCCCTCCCCGTCTCTCTCCCCGCCGCCGCCCTCTC
GGGGGGAGGGGGCGTGGGGCAGGGAGCCGATTGATGCGGCCGCCGCCGCTG
CCTGAGCCGAGGCCCCGCCGCCGCCGGAGGCCCCGCCGCCGCCGCCGCTG
CGGCCCCCATGCCCTGGCGGCCCTGGGGGGCGAAGGTGAAGATCGGCTCTAG
GATGAGTGAAGGGGCGCCGGTGCCTCGCCACCTGGTGCCGCTTCGGCAGCCGCC
CTCAGCCGAGGAGGGCACCGCGGCCGCTGCCGGCGGCCGGCGGGCGGGGCC
CGGAGCCGGCGGAGAGGGGGCGGAACCCCCCCCAGGTTACGCTGTAGCGACT
GCATCGTGTGGAACCGGCAGCAGACGTGGTTGCTGTGCTCTGTTCACTCGCTT
CATCGGCCCTGGGCTAGCCTCATGCTGTTAAATGGATGTTAGGCTCCGTCAAG
GAGTACGTGCCACGGACTGGTGGACTCCAAGGAAATGGCCAGGACCCCTTCTCC
TCTCCAAAGGCCAGCTTCTCCAAAGGCTATGGAACACCACAACAAACACTTCTACC
ACGTCCCCCCGGCCACCCCCCTCTGCCGGCGGCCCTTCTCCAGGACGCCAACCGGA
TTAGCACCCGCTTGACCAACATCACAGGGCACCCACCCGCTTCCCTGGCACCGGT
TCCCACCGGGCTAGCCCGCTCTACACAGCACGGAACACTGCTGCCCTCCGACG
GTCTCTGTCACCCACGGGCCCTTCTCACTAGACGACAGCAGGCCGGCTCCGACCCGAT
GCCAGGAGCCCCAGTACCGAGGGATGCCCTTCTGGCCACTGCCGCTATGCTACC
TCCTCTCACCTCCACGATTCACCTCCCTCTGGACCCCTGTCACCCCTTCAGGATGTC
TGCCGCTCTCTCTCACCCCTTCACTACACACATACTCCACTGAACGATCTGAGCACTTCAA
ACCCCTGTCAGAGAACAGGACTGGCATTGTCATCAACTGATGTTGAATGTTGTGATT
GAGACCCCTGACAGGATCCATAAGCAGTCTGGTGAAGGAAGGCTACCAAGGAAGTC
CGTTGTGATCAATTCTGCCAAAACAGACTCATTTATCGGATCCAACAGACCACTT
GGGGATTGAAATTCTATGGAGAGTGAAGACGTTATCAAAGGCAGGTGCTGTCATTTCA
TGTATCATCTTGGAAATTGTCATCGTGGGATGTTCTGTCAGCATCTCACTTCAAAG
CAAAAGAACAGCTAAACAAATTCTAGGAGCACCTGAAAGAGTCACAGAATGGGAAGAA
CTACAGCCTCAAGGCATCCAGCACAAAGTCTGAGAGCTTGTGATGAAGAGCCATGTCAT
CTACAAAATTATTCAAAGGCCGATAGGCATCTGTGACTGCGCTGGAGAAAATAATGG
AGTCAGTTCTCAGCTCCCCAGTCGTTCCAGAACAGTCACTTCTGACCGAGGAAG
CCAGCCTATCAAGCACCACAGGCCAGGACAAAGGAGTGGGATGTTGCATAGGAATAC
TTTCAGAAGGGCACCCCTCACCCGAAGTCGACTGGGTGGTATTGTAAGGACAGCA
TATCAACAATTGAGAAATCAAGAATTCCAGACCAGGATACGATACCTTCCAAGGG
TAGAGGTCAGGAAGACTATATCCCACCTGCCATACAGCTGTTGTGAAAGACC
CTGGACTTTAAAGTATGTCATGGGCAATTCTGCTTCAAGAACCCAAACAAATGCAATTAAAT
ATGCAACTGCCCTCAAGAGAGAACAAACCCCTATTAAATAGCTTGGATCAAAGGACC
TGGTGGGTTATTATCCCCAAGGGCCAATTCTGCCCCATCATCCGTCATGGGTCTA
GAAGAAACCTGCAATGCCAGGGATTCTGACGTCAAAAGCATTAAATGGTCA
AAAACCTACTCCGCTGACATTGTCAGAGCAGGAGTATGCCAGTCAGTGTGTTCTA
GAAGAACACAGGAAGTGAAGGAAATTACTAGAGACTGTCAGGAACAGATCCGGATT
CTGACTGATGCCAGACGGTCAGAAGACTTCGAACTGCCAGCATGGAAGACTGAGGAC
AGTGCAGCAGAACACAGCCTTCTCCCCCTGAGTCCCAGGCCAAATCAGAACGAG
AGGCAACAAATTGTCATGAAATGAAACAAAGAGACTCTGCTAACCAAGTGA
GGAAATGAGGAATCTGCAATTATGCTTGTCAAAACAGGAAGGAGGGAAATTAA
AATACAATTATGATGATTAATTAAAGAGCATCTACTTAGAAGCC

FIG. 1

TCACCGACCTAGTGGACTCCACTAGGTCGGTGGCACGTACTCCTGACGGAGCCCAC
CACGATCCA TTGAGAACGATGAGGCAGGCCCATGCCTCTGCCGCCCTCGGG
GGCGAAGGTGAANACCGGCTCTAGGATGAGTGAAGGGGGCGGCCGTCGCC
CCTGGTGGCGCTTCGGCAGCGGCCGCCCTGGCGAGGAGGGCACCGCGGCCGTC
GGCGCGCAGCGCGGGGGGGCCCGACGGGGCGCGAAGGGGCCGAGCC
CCCCCGGGAGTTACGCTGTAGCGACTGCATCGTGTGAAACCGCAGCAGACGTGGCT
GTGGCTGGTACCTCTGTTACCGGCTCATCGGCTGGGCTAGCCTCATGCTTCTCA
AATGGATGTGGGGCTCGTCAAGGAGTACGTGCCCCACCGACCTAGTGGACTCCAA
GGGGATGGGGCAGGACCCCTTCTCTCTCCAAGCCAGCTTCCCCAAGGCCATG
GAGACCACCAACACTACCACTTCCACACGTCCCCGCCACCCCCCTCGCCGGGGTG
CCGCCTCTCCAGGACGCCAACCGGATTAGCAGCTCGCTGACCAACATCACGGGC
GCCACCTCGCTCCCCGGGACCGGGTGCCA TCGGGGCCAGCCGGCTCACACCA
GCACGGAAACACTCGGGCTCCGACGGCTCGTCCACACGGCCGTTCTCAGTA
GCAGCACGCTGGGCTCCGACCCCGGTGCCAGGAACCTCAAGTACCCAGGCAATGCC
CTCTGGCCACTTGCGGCATACGCTACCTCTCTACCTTACGATTCTACTCCCTCT
GGACCCCTGTCTCCCTTCAGGATGTCCTCTCTCTCTCTCTCTCTCTCTCT
CCACACCAACCCAGAAACTAGCACCGCCCAAATTCTACAGCACATATTCCAC
AGAGCGATCCGAGCACTCAAACCTGCCAGACAAGGACCTGCATACTGTCTCAAT
GATGGCGAGTGTCTTGATCGAAACCTGACGGGATCCATAAACACTGTGGTGCA
AAAAGGCTTACCAAGGGATCTGGTTGATCAATTCTGCCAAAAGTATTCCATCT
ATCGGATCAACAGAACCTGGGGATTGATTACATGGAGAGTGAAGAAGTTTCAAA
AGGCAGGTGCTGTCATTGATCATCTTGGATTGTATCGTGGGATGTTCTG
TGCAGCATTCTACTTCAAAAGCAAGAAAAGCTAAACAAATCCAAGAGCAGCTGAA
AGTGCACAAAATGGTAAAGGACTCACAGTCTCAAAGCTCCAGCACAATGCCAAAGTC
AGAGAACCTGGTGAAGAGCCATGTCAGCTGCCAAATTATTCAAAGGTGGAGGCA
TCTGTGACTGCATTGGAGAAAATGATGGAGTCAGTTGTGCGGCCCAAGTCATT
CCTGAGGTCCCTCTCTGACAGAGGAAGCCAGTGTCAAACACCAACAGGAGTCTAT
CCTCTGCTGCAGGCCAGGGCAAGAAGTGGCATGTCATAGGAATGCCCTCAGAAG
GACACCCCCCTCAGGCCAGGATAGGTAGGGATTGTGGGACCCAGCATATCAGCA
ACTCGAACAAATCAAGGATCCCAGACCCAGGATACGATACCTTGCACAGGATAGGGT
CAGGAAGACTATATCCACCTGCCATACAGCTGTTGTGTTGAAAGACCCCTGGAC
TTAAAGTATTCACTCCAGTGGTTAAAACCCAACGAAATACATCAATAAAATGCAAC
TGCCTCAAGAGAGACAAACCCCTATTTAATACGCTTGGAGAAAAGGACCTGGTGG
CTATTCCAAAGGGCAGTTCTGCCCATATCCCTCATGGGTTAGAGGAA
ACCTGCCCTGCAAATGCCAGGGATTCTGAAGTCAAAGCATCAAATGGTGCAAAACT
CCTATTGACTGACGTTGCAATGTGAGTATTCCAGTCAGCAGTGTCTTATAGCAGA
ACAACAAGAAGTAAAATATTGCTAGAAAAGTGTCCAGGAGCAGATCCGAATTCTGACT
GATGCCAGACGGTCAGAAGACTACGAAACTGGCCAGCGTAGAAAACCGAGGACAGTGC
AGCAGAAAACACAGCCTTCTCCCCCTGAGTCCCAGCAGCAAATCAGAAGGAGGCGC
ATTGGTCTTAAGAAAATGAAATACAAAGAGACTCTGCATTGACCAAGTGAATTGAGAT
GTAGGAATCTGTCATTCTGCTTGTCAACAGGAAAGAGGAGGAAATCAAATACAA
ATTATTATATGCTTAAAGAGCATCTACTTGAAGAAAACCAAATAGTCTATGCC
CCTCATATCATAGTGTGTTTAACAAAATTTTTAAGGGAAAAGAAAATGTTCTAGGA
GGGATAAGCTT

FIG. 2

3
FIG.

hNRG3B1 1 MSEGA_nAASPPGAASAAASAE_nEGTAAAAAAGGGPDGGGE_nEPRA
mNRG3 1 MSEGA_nAASPPGAASAAASAE_nEGTAAAAAAGGGPDGGGE_nPPR

hNRG3B1 51 E LRCSDCIVWNRQQTWLCVVPFLIGFIGLGLSMLLKWIIVGSVKEYVPT
mNRG3 51 E LRCSDCIVWNRQQTWLCVVPFLIGFIGLGLSMLLKWIIVGSVKEYVPT

H φ

↑

↓

S/T rich

↑

↓

hNRG3B1 101 PLVDSKGMDQDPFFLSKPKSSFPKAWE TTTTTTTSPATPSAGGAASSRT
mNRG3 101 PLVDSKGMDQDPFFLSKPKSSFPKAWE TTTTTTTSPATPSAGGAASSRT

↑

↓

hNRG3B1 151 PNRISTRALTTITRAPTRFPGHRVPIRASPRSTARTAAPPATVPSSTTAAPF
mNRG3 151 PNRISTRALTTITRAPTRFPGHRVPIRASPRSTARTAAPPATVPSSTTAAPF

hNRG3B1 201 FSSSTI[FSRPPVFGTSQAMPWPTAAAYATSYLYHDSTPSWTLSPFQQD
mNRG3 201 FSSSTI[FSRPPVFGAPSQAMPWPTAAAYATSYLYHDSTPSWTLSPFODA

hNRG3B1 250 - A S S S S S S S S A T T T T P E T S T S P K F H T T T Y S T E R S E H F K P E R O K D L A Y E
mNRG3 251 A A S S S S P S S T S S T T T T P E T S T S P K F H T T T Y S T E R S E H F K P E R O K D L A Y E

hNRG3B1 289 [NDGEFFVIETLTGSHKHKEGYQGVREDOFLPKTDSSISDPTDHLG
mNRG3 301 NDGEFFVIETLTGSHKHKEGYQGVREDOFLPKTDSSISDPTDHLG

FIG. 4A-1

hNRG3B1 349 F F M E S E E V Y O R O V L S I C I F G I V I V G M F C A A F Y F K S K K Q A K O I Q E Q [KV
 mNRG3 351 F F M E S E D V Y O R O V L S I C I F G I V I V G M F C A A F Y F K S K K Q A K O I Q E H [KE

hNRG3B1 398 P Q N G K S Y S L K A S S T M A K S E N [V K S H V Q [Q N Y S K V E F H P V T A L E K M W E S S F
 mNRG3 401 S Q N G K N Y S L K A S S T - [K S E S L [M K S H V H [Q N Y S K A D R H P V T A L E K I W E S S F

hNRG3B1 449 V G P Q S F P E V P [S P D R G S Q S V K H H R S L S S C C S P G Q R S G M L H R N A F R R I P S P
 mNRG3 449 S A P Q S F P E V T [S P D R G S Q P I K H H S P G Q R S G M L H R N T F R R A P P S P

hNRG3B1 498 F S R L G G I V G P A Y Q Q L E E S R I P D Q D T I P C Q G I E V R K T I S H L P I Q L W C V E R P
 mNRG3 492 F S R L G G I V G P A Y Q Q L E E S R I P D Q D T I P C Q G I E V R K T I S H L P I Q L W C V E R P

hNRG3B1 549 [D L K Y S S S S L K T Q R N T S I N M Q L P S R E T N P Y F N S L E [P K D L V G Y S S T R A S S V
 mNRG3 542 [D L K Y V S N C L R T Q Q V A S I N M Q L P S R E T N P Y F N S L D [P K D L V G Y L S P R A N S V

hNRG3B1 588 P I P S V G L E E T C L Q W P G I S E V K S I K W C K N S Y S A D V V N V S I P V S D C L I A E Q
 mNRG3 592 P I P S M G L E E T C M Q W P G I S D V K S I K W C K N S Y S A D V V N A S I P V S D C V I E E Q

hNRG3B1 649 D E V K I L L E T V Q E Q I R I L T D A R R S E D Y E L A S V E T E D S A S E N T A F L P L S P T A
 mNRG3 642 D E V K I L L E T V Q E Q I R I L T D A R R S E D F E L A S M E T E D S A S E N T A F L P L S P T A

hNRG3B1 699 K S E R E A Q F V L R N E I Q R D S A [TK
 mNRG3 692 K S E R E A Q F V L R N E I Q R D S V [TK

FIG. 4A-2

| | | | | |
|--------|-----|---|----------|---|
| hNG3B1 | 1 | WSEGAAASPPGAAASAAAAAEEGTAAAAAAAAAGGGPDGGEGAAEPPR | | |
| hNG3B2 | 1 | WSEGAAASPPGAAASAAAAAEEGTAAAAAAAAAGGGPDGGEGAAEPPR | | |
| | | | HΦ | → |
| hNG3B1 | 51 | ELRCSDCIVWNROOTWLCVVPLFIGFIGLGLSMLLKWIIVGSVKKEYVPT | | |
| hNG3B2 | 51 | ELRCSDCIVWNROOTWLCVVPLFIGFIGLGLSMLLKWIIVGSVKKEYVPT | | |
| | | | S/Trich | → |
| hNG3B1 | 101 | DLVDSKGMGQDPFFLSKPSSFPKAWEETTTTTTSPATPSAGGAASSRT | | |
| hNG3B2 | 101 | DLVDSKGMGQDPFFLSKPSSFPKAWEETTTTTTSPATPSAGGAASSRT | | |
| | | | | |
| hNG3B1 | 151 | PNRISTRLLTITRAPTRFPGHAVPIRASPRSTIARNTAAPATVPSITTAAPF | | |
| hNG3B2 | 151 | PNRISTRLLTITRAPTRFPGHAVPIRASPRSTIARNTAAPATVPSITTAAPF | | |
| | | | | |
| hNG3B1 | 201 | FSSSTLGSRRPPVPGTFSWTOAMPWSWPTAAATSSYLDHOSTPSWTLSPFQDA | | |
| hNG3B2 | 201 | FSSSTLGSRRPPVPGTFSWTOAMPWSWPTAAATSSYLDHOSTPSWTLSPFQDA | | |
| | | | EGF-like | → |
| hNG3B1 | 251 | ASSSSSSSSATTTPEITSPKFHTTITYSTERSEHFKPCRDOKLAYCLN | | |
| hNG3B2 | 251 | ASSSSSSSSATTTPEITSPKFHTTITYSTERSEHFKPCRDOKLAYCLN | | |
| | | | | |
| hNG3B1 | 301 | DGECEFVIETLIGSHKHCRCKEQQGVRCDQFLPKTDSILSDOPTDHLGIEF | | |
| hNG3B2 | 301 | DGECEFVIETLIGSHKHCRCKEQQGVRCDQFLPKTDSILSDOPTDHLGIEF | | |

FIG. 4B-1

TM

hNG3B1 361 W E S E E V Y Q R Q V L I S C I I F G I V I V G W F C A A F Y F K S K K Q A K O I Q E Q L K V P Q
hNG3B2 361 W E S E E V Y Q R Q V L I S C I I F G I V I V G M F C A A F Y F K S K K Q A K Q I Q E Q L K V P Q

hNG3B1 401 N G K S Y S L K A S S T M A K S E N L V K S H V O L O N Y S K V E R H P V T A L E K M M E S S F V G
hNG3B2 401 N G K S Y S L K A S S T M A K S E N L V K S H V O L O N Y S K V E R H P V T A L E K M M E S S F V G

hNG3B1 451 P O S F P E V P A S P D R G S O S V K H R S L S C C S P G Q R S G M L H R N A F R R T P P S P R S
hNG3B2 451 P O S F P E V P A S P D R G S O S V K H R S L S C C S P G Q R S G M L H R N A F R R T P P S P R S

hNG3B1 501 R L G G I V G P A Y Q Q L E E S R I P D Q Q T I P C Q G | E V A R K T I S H L P I Q L W C V E R P L D
hNG3B2 501 R L G G I V G P A Y Q Q L E E S R I P D Q Q T I P C Q G

hNG3B1 551 L K Y S S S G L K T O R N T S I N W O L P S R E T N P Y F N S L E Q K D L V G Y S S T R A S S V P |
hNG3B2 529 . Y S S S G L K T O R N T S I N W O L P S R E T N P Y F N S L E Q K D L V G Y S S T R A S S V P |

hNG3B1 601 I P S V G L E E T C L O M P G I S E V K S I K W C K N S Y S A D O V V N Y S I P V S D C L I A E Q Q E
hNG3B2 577 I P S V G L E E T C L O M P G I S E V K S I K W C K N S Y S A D O V V N Y S I P V S D C L I A E Q Q E

hNG3B1 651 V K I L L E T V Q E Q I R I L T D A R R S E D Y E L A S V E T E D S A S E N T A F L P L S P T A K S
hNG3B2 627 V K I L L E T V Q E Q I R I L T D A R R S E D Y E L A S V E T E D S A S E N T A F L P L S P T A K S

hNG3B1 701 E R E A Q F V L A N E I O R D S A L T K
hNG3B2 677 E R E A Q F V L A N E I O R D S A L T K

FIG. 4B-2

FIG. 5

| | | |
|-------------|-----|---|
| hNRG3.egf | 288 | [H] F K P C R D K D L A Y C L N D G E C F V I E T [T] G S H K H - . |
| cAFIA.egf | 137 | [H] L T K C D I K Q K A F C V N G G E C Y M W K D L P N P P R Y L C R C P N E F T G D R C - Q N Y V |
| hAR.egf | 142 | [K] K N P C N A E F Q N E C I H - . G E C K Y I E H L E A V T - - - C K C Q Q E T F G E R C G E K S M |
| hBTC.egf | 65 | [H] F S R C P K O Y K H Y C I K - . G R C R F V Y V A E Q T P S - - - C V C D E G Y I G A R C E R V D L |
| hEGF.egf | 972 | S D O S E C P L S H D G Y C L H D G Y C M Y I E A D K Y A - - - C N C V V G Y I G E R C Q Y R D L |
| hHB-EGF.egf | 104 | K A D P C L R A Y K D F C I H - . G E C K Y V K E L R A P S - - - C I C H P G Y H G E R C H G L S |
| hHRGα.egf | 178 | [H] L V K C A E K E K T F C V N G G E C F M V K D L S N P S R Y L C K C Q P G F T G A R C T E N Y P |
| hHRGβ.egf | 178 | [H] L V K C A E K E K T F C V N G G E C F M V K D L S N P S R Y L C K C Q P N E F T G D R C - Q N Y V |
| hTGFr.egf | 43 | H F N D C P D S H T Q E C F H - . G T C R F L V Q E D K P A - - - C V C H S G Y Y G A R C E H A D L |
| mEPF.egf | 57 | Q I T K C S S D M D G Y C L H - . G A C I Y L V D M R E K F - - - C R C E V G Y T G L R C E H F F L |

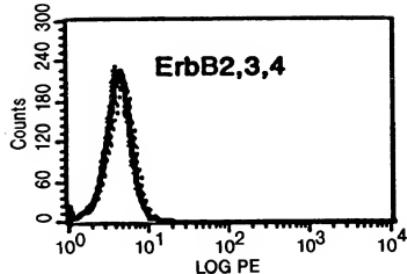


FIG. 6A

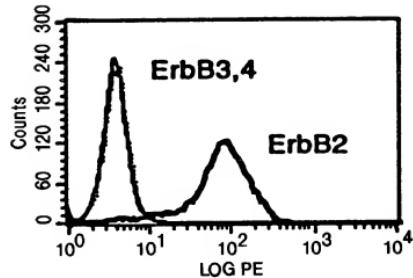


FIG. 6B

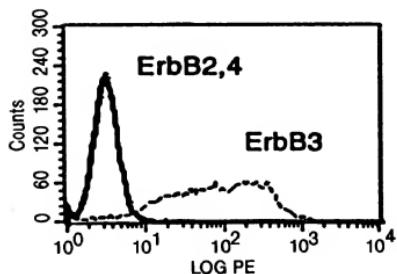


FIG. 6C

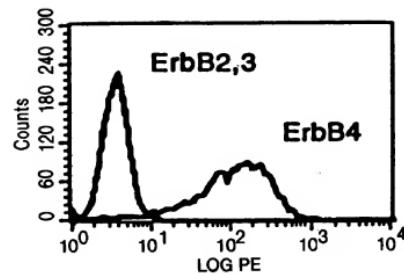


FIG. 6D

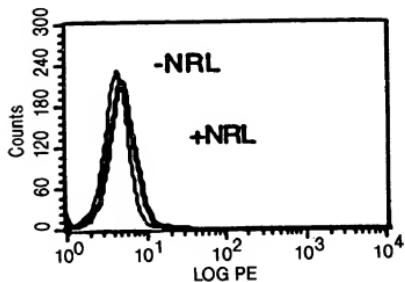


FIG. 6E

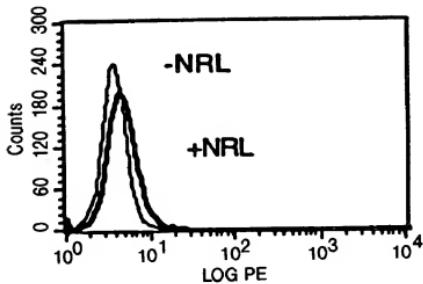


FIG. 6F

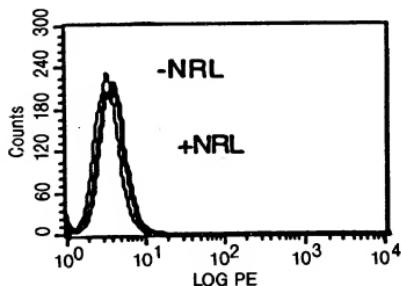


FIG. 6G

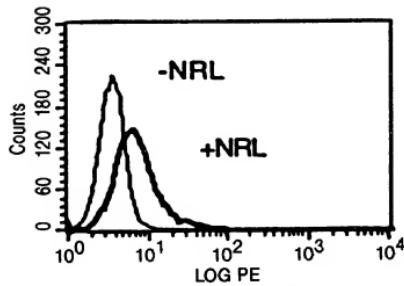


FIG. 6H

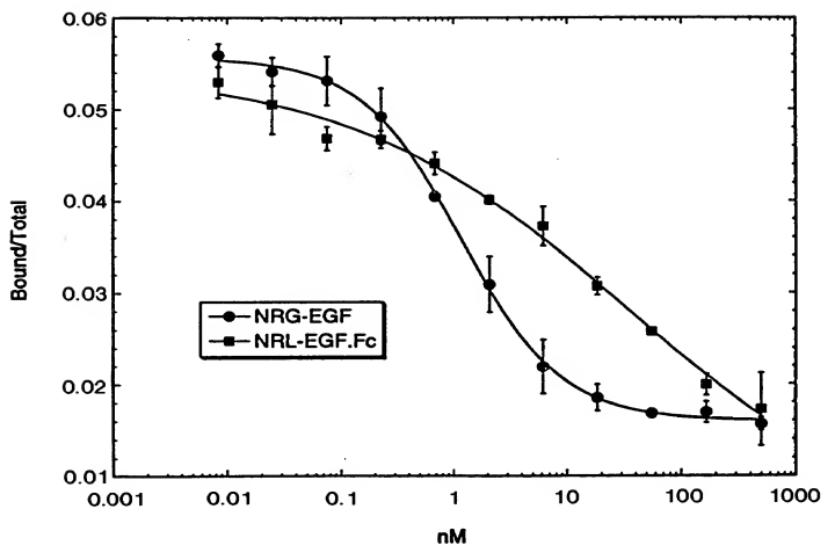


FIG. 7